

REMARKS

Claims 11, 12, 14 to 18 and 23 to 20 as set forth in Appendix I of this paper are herewith presented for further prosecution in this case. Claims 11, 12, 14, 15 and 26 to 29 have been revised relative to the version of claims previously before the Examiner as indicated in the listing of the claims.

More specifically, applicants have corrected inadvertent errors in Claims 14 and 15 which were noted in the claim objections. Accordingly, it is respectfully requested that the claim objections be withdrawn. Additionally, applicants have revised Claims 11, 12 and 26 to 29 for clarity. No new matter has been added.

The Examiner rejected Claims 11, 12, 14, 16 to 18 and 23 to 30 under 35 U.S.C. §103(a) as being unpatentable in light of the teaching of *Estabrook et al.* (Methods Encym. 272, 44-50 (1996)) when taken in view of the disclosures of *Creaser et al.* (J. Am. Chem. Soc. 99:9, 3181-3182 (1979)), *Fish et al.* (Talanta, 44, 939-945 (1997)), *Reipa et al.* (US 6,126,795) and *Oliver et al.* (Biochem. 36, 1567-1572 (1997)).

In rejecting claims under 35 U.S.C. §103, it is incumbent upon the examiner to establish a factual basis to support the legal conclusion of obviousness.²⁾ “Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.”³⁾ In determining the scope and content of the prior art, the references have to be considered as a whole and have to be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.⁴⁾ While noting that the analysis under 35 U.S.C. §103 “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ,”⁵⁾ the Supreme Court cautioned, however, that “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articu-

2) *In re Fine*, 837 F.2d 1071, 1073, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

3) *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

4) *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

5) *KSR Int'l v. Teleflex Inc.*, 127 S.Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

lated reasoning with some rational underpinning to support the legal conclusion of obviousness.”⁶⁾ As stated in *In re Ochiai*, “section 103 requires a factintensive comparison of the claimed process with the prior art rather than the mechanical application of one or another per se rule.”⁷⁾ Only if the examiner’s burden is met, the burden then shifts to the applicant to overcome the *prima facie* case with argument and/or evidence.

It is respectfully urged that the Examiner has failed to establish a *prima facie* case of obviousness, and that the Examiner’s reasoning lacks the rational underpinning which is necessary to support a legal conclusion of obviousness. Moreover, the Examiner’s analysis of the references is deemed to be based on error for failing to consider the references as a whole for what they reasonably conveyed to a person having ordinary skill at the time applicants made their invention.

The Examiner asserted that a person of ordinary skill in the pertinent art would have been motivated to replace the electrode system which is utilized in the procedure disclosed by *Estabrook et al.* because *Reipa et al.* and *Fish et al.* point to a number of disadvantages involved in using electrode systems in an environment which comprises organic matter and/or proteins. *Fish et al.*, in fact, disclose that the fouling of Cd ion specific electrodes may be prevented by covering the electrode with a dialysis membrane. Notably, however, *Estabrook et al.* specifically state that the reactions were conducted using “[a] membrane-covered oxygen electrode ... ”⁸⁾ As such, the disclosure of *Fish et al.* cannot reasonably be deemed to motivate a person having ordinary skill to replace the electrode system employed by *Estabrook et al.* by a non-electrode bound source of electrons such as a metal powder, let alone zinc powder. The disclosure of *Reipa et al.* is equally unsuited to support the Examiner’s respective position. While it is true that col. 2, lines 34 to 55, of the reference upon which the Examiner relied mention a number of problems which may arise in certain direct and indirect oxygenase driven reactions, the authors indirectly acknowledge that those are not problems which are encountered in the process of *Estabrook et al.* when stating

Faulkner et al. (Proc. Natl. Acad. Sci. USA, 92, 7705-7709, 1995) have shown mediated, electrode-driven biocatalysis using cobalt(III) sepulchrate to transfer electrons to rat recombinant liver P450 fusion proteins. In these mediated biocatalysis studies, the electrolysis enzyme turnover rate was comparable with the NADPH-driven cycle for a number of recombi-

6) *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

7) 71 F.3d 1565, 1571, 37 USPQ2d 1127, 1132 (Fed. Cir. 1995).

8) Page 46, lines 6 to 10, of *Estabrook et al.*

nant fusion microsomal P450 enzymes. See also Estabrook et al. (Methods in Enzymology, Cytochrome P450, Part B, eds. Johnson & Waterman, 44-50, 1996). The drawback to this method is the use of the cobalt mediator, which is expensive and difficult to remove from the reactants and products.^[9]

Rather than providing for a motivation to replace the electrode system of *Estabrook et al.* as the Examiner would have it, the references in fact corroborate that there was no incentive or motivation for a person having ordinary skill in the pertinent art to replace the electrode system. The disclosure of *Fish et al.* clearly shows that the membrane-covered electrode used by *Estabrook et al.* avoided fouling problems, which is further corroborated by the fact that *Reipa et al.* do not address the process of *Estabrook et al.* when discussing numerous electrode-related problems encountered in the background art but rather points to mediator-related problems which may be encountered when employing the process of *Estabrook et al.* The Examiner's argument that "[o]ne of ordinary skill in the art would have been motivated to use Zn dust as a source of non-electrode bound electrons because ... *Reipa et al.* teaches disadvantages of a system using electrodes and P450 enzymes in hydroxylating organic compounds (irreversible adsorption of protein constituents leading to electrode fouling and protein denaturation) thus decreasing its efficacy, and *Fish et al.* teaches that electrode fouling due to organic matter is a problem well known in the art,"¹⁰⁾ therefore lacks reasonably support in the references upon which the Examiner relied.

The Examiner further asserted that "it would have been obvious to one having ordinary skill in the art to modify the method of *Estabrook et al.* in hydroxylating fatty acids at the ω [lacuna] by using ... Zn dust as the non-electrode source of electrons [sic] as taught by *Creaser et al.* One of ordinary skill in the art would have been motivated to use the mutant cytochrome P450 monooxygenase of *Oliver et al.* because said mutant is able to catalyze ω hydroxylation of fatty acids. One of ordinary skill in the art would have been motivated to use Zn dust as a source of non-electrode bound electrons because *Creaser et al.* teaches that Zn dust causes immediate reduction, Zn dust is widely available (Sigma),"¹¹⁾ and that "[o]ne of ordinary skill in the art would have had a reasonable expectation of success since *Estabrook et al.* teaches a method of hydroxylating fatty acids with cytochrome P450 monooxygenases by replacing NADPH with an electrochemically generated reduction by the mediator Co(III) sepulchrate, *Creaser et al.* teaches a method of generating two electrons using the mediator Co(III) sepulchrate and Zn dust as the source of electrons, and *Oliver*

9) Col. 2, indicated lines 56 to 67, of US 6,126,795, emphasis added.

10) Office action page 5, lines 13 to 20.

11) Office action page 5, lines 7 to 15.

et al. teaches a mutant that catalyzes ω hydroxylation of fatty acids."¹²⁾ Applicants respectfully disagree.

As previously pointed out by applicants, the disclosure of *Creaser et al.* lacks any guidance, teaching or suggestion to employ a combination of zinc dust and Co(III) sepulchrate in the context of a biochemical system, i.e., in the presence of organic matter or proteins. There is no experimental guidance nor is there hypothetical guidance in the reference. To the contrary, at the end of the reference, it is speculated to use in organic and inorganic chemistry to use as therapeutic agents – still without any experimental guidance. *Creaser*; p. 3182, right col. 2nd paragraph. Potential biochemical applications are not at all taught, suggested or even implied. Also, considering the problems addressed in the section of *Reipa et al.* upon which the Examiner relied, i.e., the possibility of irreversible absorption of protein constituents leading to fouling of the surface and protein denaturation, a person of ordinary skill in the pertinent art clearly had no reasonable expectation that a combination of zinc dust and Co(III) sepulchrate could be successfully employed in the process of *Estabrook et al.* instead of the membrane-covered electrode.

As such, neither the references upon which the Examiner relied nor the Examiner's arguments can be deemed to establish that the subject matter of applicants' claims was *prima facie* obvious at the time applicants made their invention. The Examiner, therefore, has not met her burden, and the burden is not on applicants to overcome a *prima facie* case by presenting evidence.

Nonetheless, applicants have compared in an additional experiment the reaction rates for the BM-3 mutant F87A by applying an electron donor system representative of the claimed subject matter and comparing with conditions similar to those in the cited art (electron source NADPH), and the data were presented by applicants with the paper dated February 12, 2004. An artificial substrate 12-pNCA was used as the enzyme substrate to measure activity via an optical test. Said specific substrate was used because the mutant had been adapted by the mutation to the optimum conversion of fatty acids of medium chain length (see Table 4 on page 47 of the application which shows 100% conversion of 12-pNCA for mutant F87A but merely 33% for the BM-3 wild-type). As apparent from the data in Table 4, the specific mutant may influence the substrate specificity of the enzyme as it modifies the design of the substrate pocket of the enzyme. The modification has no impact on the reactive center and consequently no influence on the redox process involved in the reaction. Consequently it is scientifically reasonable to compare the mutant data generated by applicants with the data already disclosed by *Estabrook et al.* (see Table I, p.46 of *Estabrook*

12) Office action page 5, line 20, to page 6, line 4.

et al.) as long as the same reference (here NADPH as electron source) is applied in each of the experiments. With the NADPH reactions set to 100%, the results showed that Zn dust and Co(III) sepulchrate reaction had a relative reaction almost twice as high as that of the example of *Estabrook et al.* The respective data will be presented in form of a duly executed Declaration for the Examiner's perusal as soon as such Declaration becomes available. These data show that applicants' method which requires a particular electron donor system of a metal powder and a mediator is considerably better suited for the enzyme reactions than the system employed in the process taught by Estabrook et al. Such distinctly superior results could not be expected on the basis of the references cited by the Examiner and/or the knowledge of one having ordinary skill the art at the pertinent time

Therefore, the subject matter of Claims 11, 12, 14, 16 to 18 and 23 to 30 cannot be considered to be rendered unpatentable under Section 103(a) by the teaching of *Estabrook et al.* when taken in view of the disclosures of *Creaser et al.*, *Fish et al.*, *Reipa et al.* and *Oliver et al.*

It is respectfully requested that the Examiner reconsider her position and that the rejection be withdrawn. Favorable action is solicited.

Additionally, the Examiner rejected Claims 11, 12, 14 to 18 and 23 to 30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable in light of Claims 1 to 5 of *US 7,531,335* to *Hauer et al.* when taken in view of the disclosures of *Estabrook et al.*, *Creaser et al.*, *Fish et al.* and *Reipa et al.*

According to long-standing holdings of the Courts, a double patenting rejection of the obviousness type is analogous to a failure to meet the non-obviousness requirement of 35 U.S.C. §103 except that the reference underlying the double patenting rejection is not considered prior art. Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. §103 obviousness determination.¹³⁾ While the determination underlying the obviousness-type double patenting analysis is made with a view to the claimed invention rather than the disclosure of the reference underlying the obviousness-type double patenting rejection, the specification can always be used as a dictionary to learn the meaning of a term in the earlier claim.¹⁴⁾ Also, those portions of the specification which provide support for the earli-

13) *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Braat*, 837 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991).

14) *In re Boylan*, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968).

lier claims may be examined and considered when addressing the issue of whether a claim in the application defines a variation of an earlier claimed invention.¹⁵⁾

Similar to the foregoing issue, the Examiner relied on the disclosures of *Fish et al.* and *Reipa et al.* as allegedly showing why a person of ordinary skill in the pertinent art would have been motivated to replace the electrode system of *Estabrook et al.*'s process by a combination of zinc powder and Co(III) sepulchrate, and alleged that a person of ordinary skill in the art would have had a reasonable expectation that the process would nonetheless be successful. However, as addressed in the foregoing, neither *Fish et al.* nor *Reipa et al.* support the Examiner's allegation, and the references also fail to support a reasonable expectation of success.

Again, neither the art upon which the Examiner relied nor the Examiner's arguments reasonably support that the subject matter of applicants' claims would have been *prima facie* obvious in view of the combination of *Hauer et al.* when taken in view of the disclosures of *Estabrook et al.*, *Creaser et al.*, *Fish et al.* and *Reipa et al.* It is therefore respectfully requested that the rejection of Claims 11, 12, 14 to 18 and 23 to 30 under the judicially created doctrine of obviousness-type double patenting be withdrawn. Favorable action is solicited.

15) *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).